REMARKS

Claims 2, 3, 12-21, and 35-38 stand rejected "over the combined teachings" of U.S. Pat. 5,484,601 to O'Leary *et al.* ("O'Leary"), U.S. Pat. 5,385,587 to Yim *et al.* ("Yim"), and U.S. Pat. 6,030,635 to Gertzman *et al.* ("Gertzman"). Claim 2 is independent.

Applicants thank the Examiner for providing an interview with Applicants' representative on August 15, 2003. The patentability of the pending claims was discussed.

Applicants have discovered a bone graft substitute composition that has an extended set time and "sufficient robustness to withstand fluid impact with minimal erosion." See page 4, lines 2-4 of the application. The composition generally includes four ingredients: (1) calcium sulfate, as a matrix material; (2) a mixing solution, such as sterile water or saline solution; (3) a cellulose derivative such as carboxymethylcellulose, which acts as a plasticizer; and (4) demineralized bone matrix ("DBM"), which can act as an osteogenic factor. See page 4, lines 17-20, page 5, lines 21-24, and page 6, lines 12-15 of the application. As explained in "Preferred Embodiment 1" in the application, the preferred composition has good handability, ejectability, and robustness. See page 6, line 21 - page 7, line 12 of the application.

Claim 2 features a bone graft substitute composition including calcium sulfate, a mixing solution, a cellulose derivative, and demineralized bone matrix. The four ingredients required by claim 2 have been used previously in various and independent bone repair compositions, but never in combination. The Examiner's position, basically, is that because the ingredients have been used previously in such compositions, it would have been obvious to combine them together in one composition. However, none of O'Leary, Yim and Gertzman do nor suggest, and in fact teach away from, making this combination.

Claims 2, 3, 12-19, 21, and 35-38

Gertzman

Gertzman is the most recent of the three prior art references relied on by the Examiner. Gertzman was filed in 1998 and describes the state of the art of bone repair compositions as of 1998. Gertzman begins by describing the need for bone graft composition (col. 1, lines 14-24):

> Malleable putty is used to correct surgical defects that may be caused by trauma, pathological disease, surgical intervention or other situations where defects need to be managed in osseous surgery. It is important to have the defect filler in the form of a stable, viscous putty to facilitate the placement of the bone growth medium into the surgical site which is usually uneven in shape and depth. The surgeon will take the putty on a spatula or other instrument and trowel it into the

site or take it in his/her fingers to shape the bone inducing material into the proper configuration to fit the site being corrected.

Gertzman then discusses the problems of prior art bone repair compositions. One composition included "autologous bone particles" recovered from patients. The bone particles apparently worked fine to fill defects, but the need to collect the autologous bone particles from patients made the approach undesirable. See col. 1, lines 24-36.

A second composition described in Gertzman included an inorganic material, for example, calcium sulfate, in place of autologous bone particles. The inorganic material provided a matrix for the growth of new bone at a surgical site. But Gertzman explained that inorganic materials like calcium sulfate had characteristics that made them undesirable for use in bone repair compositions (col. 1, lines 42-47) (emphasis added):

> Calcium sulfate or plaster of Paris may be mixed with water to similarly form a putty. These inorganic materials are osteoconductive but <u>are bioinert and do not absorb or become remodeled into natural bone. They consequently remain in place indefinitely as a brittle, foreign body in the patient's tissue.</u>

According to Gertzman, demineralized bone is a good substitute for autologous bone because it is readily available. It also is "osteoinductive" and "osteoconductive." Moreover, unlike the calcium sulfate materials discussed by Gertzman, demineralized bone "is fully incorporated in the patient's tissue by a well-established biological mechanism." See col. 1, lines 48-59.

After touting the advantages of demineralized bone for use in bone repair compositions, Gertzman describes a gel product -- GRAFTON® -- that includes the demineralized bone and glycerol. But Gertzman explains that glycerol causes the composition to become "runny" and "to flow away from the [surgical] site almost immediately after placement." See col. 2, lines 28-52. Gertzman asserts that he solved the "runny" problem of GRAFTON® by combining demineralized bone with a very high molecular weight "hydrogel." Gertzman also says that "medically useful substances", such as collagen and antibiotics, can be included in the composition.

Thus, Gertzman teaches that in 1998 calcium sulfate had disadvantages when used in bone repair compositions. Gertzman further teaches that demineralized bone was a good alternative to calcium sulfate, particularly when used in combination with a high molecular weight hydrogel.

O'Leary

O'Leary was filed long before Gertzman and appears to describe GRAFTON®.[1]

O'Leary describes a bone repair composition including demineralized bone and a polyhydroxy compound like glycerol. The composition optionally may include "thixotropic agents, medicaments, and the like." See col. 1, lines 36-47. O'Leary subsequently mentions two cellulosic derivatives in a list of potential thixotropic agents. See col. 3, line 38-col. 4, line 6.

O'Leary provides an extensive list of optional "medicaments, and the like." For convenience, the list is provided below (col. 2, line 56-col. 3, line 12):

> Substances which can be readily incorporated in the bone particles in this or any other suitable manner include antiviral drugs, e.g., those suitable for preventing transmission of acquired immune deficiency syndrome (AIDS); antimicrobials and/or antibiotics such as erythromycin, bacitracin, neomycin, penicillin, polymyxin B, tetracyclines, viomycin, chloromycetin and streptomycins, cefazolin, ampicillin, tobramycin, clindamycin and gentamycin, etc.; amino acids, peptides, vitamins, inorganic elements, co-factors for protein synthesis; hormones; endocrine tissue or tissue fragments; synthesizers; enzymes such as collagenase, peptidases, oxidases, etc.; polymer-cell scaffolds with parenchymal cells; angiogenic drugs and polymeric carriers containing such drugs; collagen lattices; biocompatible surface active agents; antigenic agents; cytoskeletal agents; biologically active components such as bone morphogenetic proteins (BMPs), transforming growth factor (TCF-beta), insulin-like growth factor (IGD-1); mesenchymal elements; bone digesters; antitumor agents; cellular attractants and attachment agents; immunosuppressants; permeation enhancers, e.g., fatty acid esters such as the laurate, myristate and stearate monoesters of polyethylene glycol, enamine derivatives, alpha-keto aldehydes, etc.; and, nucleic acids.

The substances in the list generally have some type of biological activity. "Inorganic elements" is one item listed, but no examples of inorganic elements are provided.

The Examiner has taken the reference of "inorganic elements" in O'Leary's long laundry list as a reason that a person of ordinary skill in the art would have been motivated to add calcium sulfate to O'Leary's composition. But this is a pure hindsight rationale that makes no sense, for a number of reasons.

First, according to Gertzman, demineralized bone is used in bone graft compositions as a replacement for calcium sulfate. In fact, as Applicants explained previously, Gertzman teaches

[1]Note the assignee of O'Leary is Osteotech, and Gertzman mentions that GRAFTON® is a trademark of Osteotech. See col. 2, lines 33-38.

that calcium sulfate had characteristics that made it unsuitable for use in bone graft compositions and that demineralized bone-based compositions were developed to address the problem.

Second, calcium sulfate had been used in bone repair compositions (see background in Gertzman) prior to O'Leary's work to develop GRAFTON®. Given the lengthy laundry list of optional substances provided by O'Leary, if O'Leary thought there was any reason to include calcium sulfate in his composition he would have mentioned calcium sulfate in the laundry list.

Third, the specific substances included in the laundry list generally have some type of biological activity. Thus, O'Leary's composition is serving as a carrier for the substance. The substances include things like antibiotics, growth factors, bone digesters, and permeation enhancers. Calcium sulfate does not have a biological activity. In fact, as Gertzman explained in his background section, calcium sulfate can be a biological nuisance. Whatever O'Leary meant by "inorganic element," he plainly did not mean a biologically inert substance like calcium sulfate.

Fourth, and finally, compositions that include calcium sulfate generally are water-based; water causes calcium sulfate to harden. But O'Leary's composition, like GRAFTON®, are polyol-based. A person of ordinary skill in the art would be led away from including calcium sulfate in O'Leary's composition for this reason as well.

Yim

Yim teaches a composition that is used to deliver osteogenic proteins to induce bone formation. The composition includes the osteogenic protein, a "porous particulate polymer matrix," autogenous blood, and calcium sulfate. Yim also says the composition optionally can include cellulosic materials as an additional osteogenic protein sequestering agent. See col. 2, lines 16-31.

Yim's composition, apparently, is an improvement on a composition disclosed prior to Yim. That composition included the osteogenic protein and the porous particulate polymer matrix. Yim does not teach that calcium sulfate has a "medicament" value; he merely is using calcium sulfate as a carrier for the osteogenic proteins and the porous particulate polymer matrix.

The composition described by O'Leary already includes a carrier, demineralized bone mixed with glycerol. To the extent a person of ordinary skill in the art would be looking to improve the O'Leary composition, that person would look for guidance to Gertzman, which describes improvements in systems including demineralized bone as a carrier, rather than to

Yim. As Applicants already explained, Gertzman teaches that demineralized bone is a better carrier than calcium sulfate. Moreover, O'Leary's composition is based largely on polyols like glycerol, not on water, and calcium sulfate generally is used in aqueous compositions.

A person of ordinary skill in the art also would not have been motivated to use demineralized bone in Yim's composition in addition to calcium sulfate. Yim -- mistakenly according to Gertzman -- touts the advantages of using calcium sulfate as the carrier. Reading Yim, a person of ordinary skill in the art would have no reason to search for an alternative carrier. Moreover, to the extent a person of ordinary skill in the art was looking to improve the carrier used by Yim, in view of the teachings of O'Leary and Gertzman, that person would replace the calcium sulfate-based system described by Yim with the demineralized bone-based system described by O'Leary or Gertzman. Finally, given that Yim's composition is water-based, and O'Leary's composition is polyol-based, a person of ordinary skill in the art looking to improve the carrier used by Yim would not look to O'Leary for guidance.

Additional Comments

Gertzman, O'Leary, and Yim as a practical matter teach two different types of bone repair compositions. One type is water-based and uses calcium sulfate as the primary carrier. The second is polyol or hydrogel-based and includes demineralized bone as the carrier. The Examiner's approach -- using hindsight to pick and choose elements from different systems to reach a claimed invention -- has been criticized repeatedly by the Court of Appeals for the Federal Circuit. For example, in W.L. Gore and Associates v. Garlock, Inc., 220 U.S.P.Q. 303, 312-13 (1983), the court explained:

> To imbue one of ordinary skill in the art with knowledge of the invention when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.

Finally, Applicants note that the Examiner points to six prior art references as evidence of the "state of the art" in what appears to be an effort to bolster the flawed 35 U.S.C. § 103(a) rejection based on Gertzman, O'Leary, and Yim. However, the Examiner has not relied on these references as a basis for rejection of the claims under 35 U.S.C. § 103(a).[2] Applicants note that

[2]It would be rather ridiculous if the Examiner added these references to the 35 U.S.C. § 103(a) rejection. In that event, the Examiner would be relying on nine references to support a rejection of a four component claim.

the Examiner's use of these "state to the art" references is reminiscent of an Examiner's "phantom prior art" criticized in Ex parte Stern, 13 U.S.P.Q. 2d 1379, 1381 (Bd. App. 1989):

> The Examiner has failed to articulate any recognizable theory to support the rejection of the appealed claim under 35 U.S.C. § 103 as unpatentable over any of these references... [T]he Examiner states on page 4 of the Answer that
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> > 'Although the prior art fails to recite a protein having such a high specific activity, such is deemed obvious relative to advances in technology that evolves [sic, evolve] more sophisticated purification processes that produces [sic, produce] such high degree of purity.' (Emphasis supplied by Board.)
>
> The Examiner should be aware that "deeming" does not discharge him from the burden of providing the requisite factual basis and establishing the requisite motivation to support a conclusion of obviousness....The Examiner's reference to unidentified phantom prior art techniques falls far short of the mark.

Claims 3 and 20

The extent to which the Examiner will go to improperly reconstruct the compositions covered by the claims is further highlighted by the rejections of claims 3 and 20. Claim 3 features a composition including "approximately 40%" of demineralized bone, and claim 20 features a composition include specific amounts of all four ingredients. The use of these specific quantities is not suggested anywhere in Gertzman, O'Leary, or Yim.

Accordingly, independent claim 2, and claims that depend therefrom, are patentable over the teachings of O'Leary, Gertzman and Yim. Applicants respectfully request reconsideration and withdrawal of this rejection.

Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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